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Review

Endovascular brachytherapy and restenosis following lower limb angioplasty: Systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Background: Restenosis is a fundamental weakness of percutaneous femoropopliteal angioplasty (PTA). The potential of endovascular brachytherapy (EVBT) to reduce restenosis has been evaluated in randomized clinical trials, but no pooled analysis has been undertaken.
Methods: A systematic review was undertaken to identify randomized controlled trials in which PTA alone was compared to PTA plus EVBT. The Pubmed and Medline databases, American Heart Association OASIS database and conference proceedings from the Peripheral Vascular Surgery Society and Vascular Society of Great Britain and Ireland were searched. Eligible studies were randomised controlled trials comparing PTA to PTA plus EVBT in human subjects with at least one clinical outcome reported (restenosis, complications, patency). Study quality was assessed by the Jadad score. Random-effects modeling was used to generate pooled effect size estimates.
Results: Six trials (687 patients) were identified. EVBT reduced 12-month restenosis rates (pooled odds ratio 0.50; 95% CI 0.301–0.836; $p = 0.008$). The benefit disappeared by 24 months. The short-term risk of new lesions elsewhere in the treated artery was significantly increased by EVBT (pooled odds ratio 8.65; 95% CI 2.176–34.391; $p = 0.002$).
Conclusions: While limited by the small sample sizes in the included trials, this analysis suggests that the early benefit of EVBT is counter-balanced by the increased risk of new lesions and the lack of medium- to long-term reductions in restenosis risk. Based upon the best available evidence, EVBT cannot be recommended for routine clinical use.

1. Introduction

The combination of over 30 years of clinical experience, and repeated demonstrations of clear therapeutic benefit in randomised studies, has cemented the role of percutaneous transluminal angioplasty (PTA) as first line therapy for most patients with peripheral arterial occlusive disease. In the short term, PTA is economically superior to open surgery, although the benefit disappears with time as re-interventions accrue.[1] PTA is plagued by relatively high rates of early to medium-term restenosis. Restenosis rates of up to 50% within two years have been reported.[2] Numerous pharmacological and mechanical therapies have attempted to reduce restenosis.[3] The process of PTA causes intimal splitting, exposing the tunica media to blood constituents. The inflammatory cascade is initiated with the migration of polymorphonuclear leukocytes and smooth muscle cells to the injury site, generating an excessive healing response. Gradually, this leads to neo-intimal hyperplasia which, along with constrictive re-modeling and elastic recoil, results in restenosis.[4] Radiation causes cell cycle arrest, preventing cell replication. The radiation source can be external (external beam radiotherapy) or internal (endovascular brachytherapy). Early experience in the coronary circulation was promising.[5,6] Its efficacy in the femoral artery has been studied in randomized trials, although these results have been limited by low participant numbers.[7–16] There have also been concerns regarding safety.[17] We undertook a systematic review and meta-analysis to determine whether EVBT reduces restenosis in randomised clinical trials comparing restenosis following PTA alone to PTA plus EVBT. In addition, we sought to determine whether EVBT is associated with increased complications, re-interventions or de novo stenoses.

2. Methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[18] In November 2010, the electronic abstract databases Pubmed and Medline were

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searched using the search terms 'angioplasty' and 'brachytherapy'. No language restrictions were used. No limits were set on the electronic searches. Manual searches were undertaken of the abstract archives of the Peripheral Vascular Surgery Society spring and winter conferences (1998–2010) and the Vascular Society of Great Britain and Ireland annual scientific meeting (2004–2010). In addition, the American Heart Association's OASIS abstract database was searched. This archive contains abstracts presented at all the major American Heart Association meetings (Sessions, International Stroke Conference, Arteriosclerosis, Thrombosis and Vascular Biology (ATVB), Basic Cardiovascular Sciences Annual Conferences (BCVS), High Blood Pressure, Quality of Care and Outcomes Research). The abstracts of potentially relevant citations were scrutinized by two assessors (DM and SRW) to determine eligibility. Studies were eligible for inclusion in the meta-analysis provided that they met each of the following criteria: randomized controlled trial, conducted in human subjects, patients randomized to femoropopliteal segment PTA or PTA + EVBT, at least one clinical outcome reported (patency rates, restenosis rates, complications). Studies conducted in animals or studies assessing the effect of EVBT on femoropopliteal stent patency were excluded. Eligibility criteria were defined in advance of the systematic review. A formal review protocol was not recorded.

Trial quality was assessed using the Jadad score.[19] The primary outcome for the meta-analysis was morphological (angiographic or duplex ultrasound) restenosis within 12 months. Patients were classified as restenosis or not using the criteria adopted by the original trial authors. The secondary outcomes for meta-analysis were: radiological restenosis within 24 months, re-intervention required within 12 months and the development of de novo arterial stenosis in the treated limb outwith the original angioplasty site. Potentially eligible trials were reviewed independently by two authors (DM and AOC). In case of disagreement, the senior author (SRW) reviewed the trial to determine eligibility. Data were extracted from the trials for each of the outcomes listed above and recorded in an Excel spreadsheet. Random-effects models were used to calculate a pooled odds ratio for each outcome measure.[20] Heterogeneity was evaluated using the Cochran Q-test. This is a null hypothesis test in which a result with a p-value <0.05 indicates the presence of significant heterogeneity between the included studies. Bias was assessed by visual inspection of funnel plots and also by the calculation of the Horbold–Egger statistic. The statistical analysis was performed using Statsdirect 2.5.7 (Statsdirect Ltd, Altrincham, United Kingdom). The 5% level was considered significant and all p-values are two-sided.

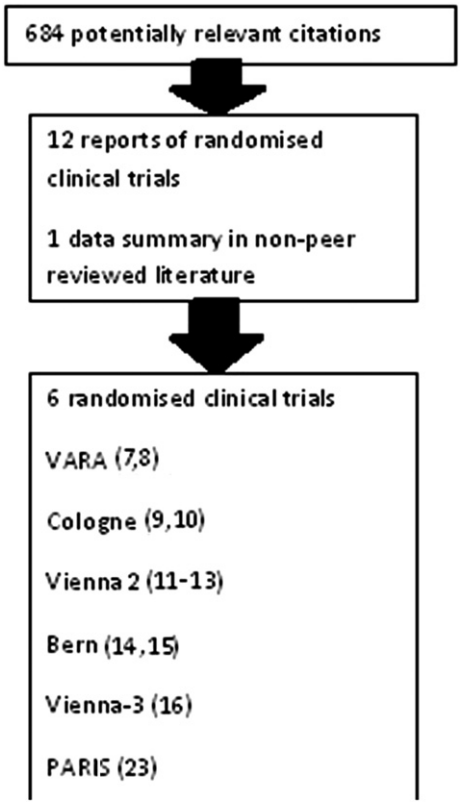

Fig. 1. PRISMA flow diagram.

Results

The results of the systematic review are summarized in Fig. 1. The initial search identified 684 potentially relevant citations. Examination of the abstracts reduced this to 12 reports of randomized clinical trials of EBVT as an adjunct to peripheral PTA.[7–16,21–23] A number of these papers reported different aspects of a single trial. Consequently, outcome data for these trials were aggregated from the various reports as follows: outcomes from the VARA trial were obtained from two separate papers[7,8]; the Cologne trial was aggregated from two separate reports[9,10]; three papers[11–13] were used to aggregate outcome data from the Vienna-2 trial; the Bern trial represents post-hoc analysis of patients recruited from a single center to two separate trials[14,15]; the Vienna-3 data were obtained from a single paper.[16] Two reports by Wyttenbach et al did not include restenosis rates.[21,22] Finally, the Peripheral Artery radiation Investigational Study (PARIS Trial) was identified from scrutiny of article bibliographies. The results of this trial have never been formally published. A synopsis was identified in a non-peer reviewed publication, from which some data were abstracted.[23] Details of the individual trials are summarized in Table 1. Overall, the six individual trials included 687 patients (343 randomized to EVBT). For clarity, the trials are referred to by name in the results, rather than by multiple citations for each. The relevant citations for each trial are listed in Table 1.

Morphological restenosis at 12 months

All six trials provided data with respect to angiographic restenosis at 12 months (VARA, Cologne, Vienna-2, Bern, Vienna-3, PARIS). There was a significant reduction in the risk of restenosis (99/343 EVBT versus 147/344 controls; pooled odds ratio 0.50; 95% CI 0.301–0.836; $p = 0.008$) (Fig. 2). There was no evidence of heterogeneity (Cochran's Q 10.09; 5 d.f.; $p = 0.07$) or bias (Egger −1.86; $p = 0.32$).

Morphological restenosis at 24 months

Data regarding angiographic restenosis at 24 months were provided by three trials (Cologne, Bern, Vienna-3). Restenosis occurred in 43/154 EVBT patients compared to 82/157 controls. However, the difference was not statistically significant (pooled odds ratio 0.32; 95% CI 0.062–1.621; $p = 0.17$) (Fig. 3). There were insufficient eligible studies to test for bias but there was evidence of heterogeneity (Cochran Q 17.27; 2 d.f.; $p = 0.0002$).

Further intervention within 12 months

Re-intervention rates within 12 months were reported by four studies (VARA, Cologne, Vienna-2, Vienna-3) (Figs. 4 and 5). Re-interventions were required in 41/171 controls compared to 25/166 EVBT patients. This difference was almost statistically significant (pooled odds ratio 0.53; 95% CI 0.272–1.017; $p = 0.06$). There was no evidence of heterogeneity (Cochran's Q 3.55; 3 d.f.; $p = 0.31$) or bias (Egger 1.92; $p = 0.22$).

De novo stenosis elsewhere in treated artery within 12 months

The development of a new stenosis elsewhere in the irradiated artery within the first year, but outside the previously irradiated zone, was reported by three trials (VARA, Cologne, Vienna-3). The findings of the original trials are summarized in Table 2. Overall, EVBT was associated with a significantly greater risk of de novo stenosis. This occurred in 16/109 EVBT versus 3/115 control patients

Table 1
Characteristics of included trials.

Trial	Inclusion criteria	Study size	EVBT protocol	Restenosis definition	Outcomes reported	Jadad score
VARA[7,8]	Patient with stenotic or totally occlusive femoropopliteal lesions ≤10 cm in length, producing claudication or non-critical limb ischaemia	60	14 Gy at predetermined points along the angioplasty segment using a centering catheter and iridium-192 source	Decrease in lumen diameter ≥50% or peak systolic velocity ratio >2.5 on duplex scan	12-Month restenosis rate 12-Month re-intervention rate De novo stenosis rate	2
Cologne[9,10]	Previously untreated femoropopliteal lesions ≤5 cm for occlusions or ≤8 cm for stenosis	30	14 Gy along the length of the angioplasty segment using a centering catheter and iridium-192 source	Diameter reduction >50% in the angioplasty segment on follow-up digital subtraction angiography	12-Month restenosis rate 12-Month re-intervention rate De novo stenosis rate 24-Month restenosis rate	2
Vienna-2[11–13]	Femoropopliteal lesion ≥5 cm for de novo stenosis or any length for recurrent lesions producing intermittent claudication or rest pain without tissue loss	113	Non-centering catheter so dose varied with catheter position; generally calculated as 12 Gy dose along length of angioplasty segment	Diameter reduction ≥50% on follow-up digital substraction angiography or peak systolic velocity increase ≥140% on duplex ultrasound	12-Month restenosis rate 12-Month re-intervention rate	3
Bern[14,15]	≥50% De novo or recurrent femoropopliteal lesion producing claudication or critical limb ischaemia	147	12 Gy or 14 Gy from an iridium-192 source depending on trial in which patient was enrolled	≥50% Diameter reduction on follow-up angiography interpreted by two blinded assessors	12-Month restenosis rate 24-Month restenosis rate	2
Vienna-3[16]	Femoropopliteal lesion ≥5 cm for de novo stenosis or any length for recurrent lesions producing intermittent claudication or rest pain without tissue loss	134	18 Gy from an iridium-192 source delivered along the length of the angioplasty site using a centering catheter	>50% Luminal diameter narrowing on follow-up angiography or peak systolic velocity ratio >2.4	12-Month restenosis rate 12-Month re-intervention rate De novo stenosis rate 24-Month restenosis rate	2
PARIS[23]	Femoropopliteal lesion	203	14 Gy from an iridium-192 source delivered to a depth of 2 mm at the angioplasty site	Not defined	12-Month restenosis rate	Not assessed

(pooled odds ratio 8.65; 95% CI 2.176–34.391; $p = 0.002$). There was no evidence of heterogeneity (Cochran's Q 0.02; 2 d.f.; $p = 0.99$). Insufficient trials were eligible to test for bias.

Sensitivity analysis

As the PARIS trial data has never been formally published, a sensitivity analysis of morphological restenosis at 12 months was undertaken in which the PARIS trial data were excluded. The apparent benefit of EVBT with respect to 12-month restenosis persisted following exclusion of the PARIS data, with a pooled odds ratio of 0.40 (95% CI 0.27–0.59; $p < 0.0001$). Cochran's Q-test remained non-significant, indicating an absence of heterogeneity (Cochran's Q 3.34; $p = 0.50$). There was no evidence of bias (Egger = −0.86; $p = 0.54$).

Discussion

Despite technical advances in balloon angioplasty since its inception, restenosis remains a fundamental weakness of the procedure. Re-stenoses occur secondary to neo-intimal hyperplasia, which is thought to be driven by an inflammatory mechanism triggered by balloon expansion of an atherosclerotic plaque. Shear stress in the vessel wall causes vascular injury, leading to release of pro-inflammatory cytokines and activation of circulating monocytes.[24] Inflammatory cells adhere to the angioplasty site, mediated in part by E-selectin.[25] Inhibition of inflammation may provide the key to reducing re-stenoses. However, brachytherapy has no demonstrable effect on a range of inflammatory mediators expressed in the first 48 h following femoropopliteal angioplasty.[26]

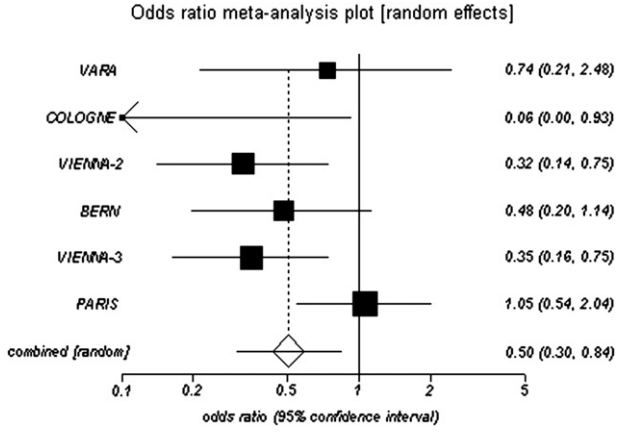

Fig. 2. Forest plot of morphological restenosis at 12 months.

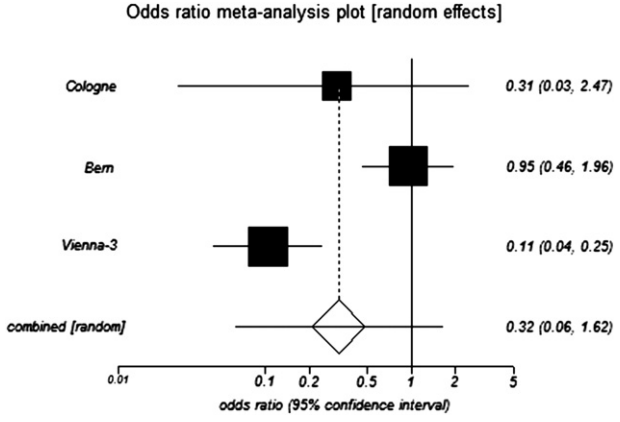

Fig. 3. Morphological restenosis within 24 months.

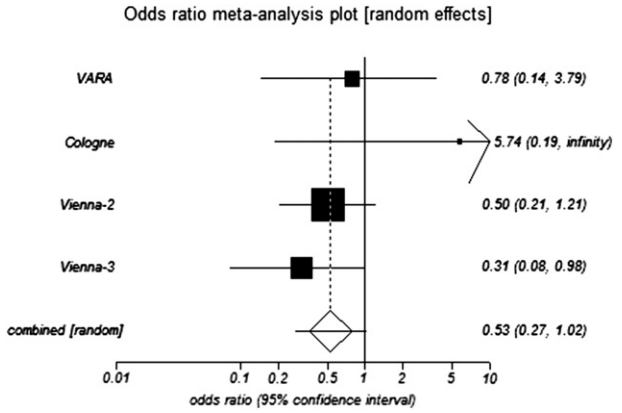

Fig. 4. Re-intervention rates within 12 months.

Table 2
Trials reporting de novo lesions within six months following EVBT.

Trial	Assessment of de novo stenoses	Definition of de novo stenosis	De novo stenosis control arm	De novo stenosis EVBT arm
VARA[7,8]	Single-plane angiography and intravascular ultrasound at 6 months	>50% Stenosis in the arterial segment immediately proximal or immediately distal to the treated segment	0/33	3/27
Cologne[9,10]	Duplex ultrasound	>30% Stenosis outside irradiated segment	3/15	4/15
Vienna-3[16]	Duplex ultrasound; digital subtraction angiography or magnetic resonance angiography	Peak velocity ratio >2.4 indicating >50% stenosis in untreated segment	1/67	7/67

The six randomized trials identified in this systematic review all reported an initial improvement in patency rates 12 months post-procedure. Only three trials reported results at 24 months, by which time the patency advantage provided by EVBT had disappeared. There were insufficient data regarding longer-term, 5-year follow-up to merit a formal meta-analysis. The Vienna-2 group reported identical restenosis rates at 5 years (72.5% in both groups).[11–13] Far from preventing medium- to late-term restenoses, the meta-analysis of all available data suggests that EVBT significantly increases the risk of de novo stenosis elsewhere in the treated artery (pooled odds ratio 8.65; 95% CI 2.176–34.391; $p = 0.002$).

Most of the trials eligible for meta-analysis achieved Jadad scores of two, indicating moderate quality. The studies suffered primarily from the inherent difficulty in blinding staff to the use of EVBT. The technique is quite cumbersome, often involving a complex transfer of a patient with femoral sheaths and catheters in situ from the interventional radiology suite to the radiotherapy suite. Blinding of subsequent outcome assessment using duplex or digital subtraction angiography was possible, but it was unclear from most reports whether this had been achieved. The individual trial arms were generally well matched in terms of co-morbidities, medication use and lesion morphology. That said, as can be seen in Table 1, the lesions included in the trials were generally short (<10 cm in length). In this pattern of localised disease, 5-year patency rates of 70% have been reported, comparable to bypass surgery. Therefore the selection criteria employed in these trials may in some way explain the apparent lack of benefit with EVBT.

There are some further limitations. Overall, the available sample size for this meta-analysis is small, totaling 687 patients. Moreover, follow-up is limited, with most of the trials only reporting follow-up to 12 or 24 months. The PARIS trial is the single largest randomised trial of EVBT in PTA. While it has been presented at major conferences, the results have never been formally published following peer review. Despite considerable efforts, we were only able to identify one non-peer reviewed publication which provides some outcome data from the PARIS trial.[23] We were unable to obtain any further data. Thus, the conclusions regarding complications and de novo restenosis must be treated with some caution, as the largest trial has never published these data. Inclusion of unpublished trials in meta-analyses is sometimes controversial. However, published trials are more likely to show a positive treatment effect than unpublished trials. Thus, systematic review and meta-analyses that fail to include relevant unpublished data risk overestimating treatment effects and further exacerbate publication bias.[27] The current analysis reports the statistical combination of the best available data from randomised clinical trials of EVBT in PTA. The best available evidence suggests that EVBT confers some short-term benefit, but at the expense of increased short-term arterial damage. The short-term damage does not appear to be offset by medium-term benefits. It appears difficult to justify further studies and therefore, one must conclude that EVBT has little clinical utility in patients undergoing PTA.

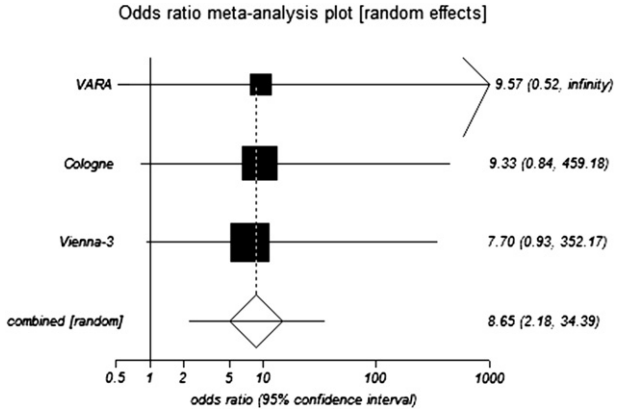

Fig. 5. De novo stenosis within 6 months.

Ethical approval
Not applicable.

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Conflicts of interest
None declared.

Author contribution

DM – systematic review, collecting data, drafting manuscript.
AOC – supervised systematic review, drafting manuscript.
EMB – systematic review.
EK – critical revision of manuscript.
SRW – study design, statistical analysis, critical revision of manuscript.

Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.ijsu.2012.02.008.

References

1. Forbes JF, Adam DJ, Bell J, Fowkes F, Gillespie I, Raab GM, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial: health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. *J Vasc Surg* 2010;**51**:43S–51S.
2. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty: factors influencing long-term success. *Circulation* 1991;**83**:I70–80.
3. Shammas NW. Restenosis after lower extremity interventions: current status and future directions. *J Endovasc Ther* 2009;**16**:I170–82.
4. Schillinger M, Minar E. Restenosis after percutaneous angioplasty: the role of vascular inflammation. *Vasc Health Risk Manag* 2005;**1**:73–8.
5. Condado JA, Waksman R, Gurdiel O, Espinosa R, Gonzalez J, Burger b, et al. Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. *Circulation* 1997;**96**:727–32.
6. King III SB, Williams DO, Chougule P, Klein JL, Waksman R, Hilstead R, et al. Endovascular beta-radiation to reduce restenosis after coronary balloon angioplasty: results of the beta energy restenosis trial (BERT). *Circulation* 1998;**97**:2025–30.
7. Hagenaars T, Po IF, van Sambeek MR, Coen VL, Van Tongeren RB, Gescher FM, et al. Gamma radiation induces positive vascular remodeling after balloon angioplasty: a prospective, randomized intravascular ultrasound scan study. *J Vasc Surg* 2002;**36**:318–24.
8. van Tongeren RB, van Sambeek MR, van Overhagen H, Coen VL, Schmitz PI, Gescher FM, et al. Endovascular brachytherapy for the prevention of restenosis after femoropopliteal angioplasty. Results of the VARA Trial. *J Cardiovasc Surg (Torino)* 2005;**46**:437–43.
9. Krueger K, Landwehr P, Bendel M, Nolte M, Stuetzer H, Bongartz R, et al. Endovascular gamma irradiation of femoropopliteal de novo stenoses immediately after PTA: interim results of prospective randomized controlled trial. *Radiology* 2002;**224**:519–28.
10. Krueger K, Zaehringer M, Bendel M, Stuetzer H, Strohe D, Nolte M, et al. De novo femoropopliteal stenoses: endovascular gamma irradiation following angioplasty–angiographic and clinical follow-up in a prospective randomized controlled trial. *Radiology* 2004;**231**:546–54.
11. Minar E, Pokrajac B, Maca T, Ahmadi R, Fellner C, Mittlböck M, et al. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty: results of a prospective randomized study. *Circulation* 2000;**102**:2694–9.
12. Pokrajac B, Pötter R, Maca T, Fellner C, Mittlböck M, Ahmadi R, et al. Intra-arterial (192)Ir high-dose-rate brachytherapy for prophylaxis of restenosis after femoropopliteal percutaneous transluminal angioplasty: the prospective randomized Vienna-2-trial radiotherapy parameters and risk factors analysis. *Int J Radiat Oncol Biol Phys* 2000;**48**:923–31.
13. Wolfram RM, Budinsky AC, Pokrajac B, Potter R, Minar E. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty: five-year follow-up – prospective randomized study. *Radiology* 2006;**240**:878–84.
14. Diehm N, Silvestro A, Do DD, Greiner R, Triller J, Mahler F, et al. Endovascular brachytherapy after femoropopliteal balloon angioplasty fails to show robust clinical benefit over time. *J Endovasc Ther* 2005;**12**:723–30.
15. Zehnder T, von Briel C, Baumgartner I, Triller J, Greiner R, Mahler F, et al. Endovascular brachytherapy after percutaneous transluminal angioplasty of recurrent femoropopliteal obstructions. *J Endovasc Ther* 2003;**10**:304–11.
16. Pokrajac B, Potter R, Wolfram RM, Budinsky AC, Kirisits C, Lileg B, et al. Endovascular brachytherapy prevents restenosis after femoropopliteal angioplasty: results of the Vienna-3 randomised multicenter study. *Radiother Oncol* 2005;**74**:3–9.
17. Bonvini R, Baumgartner I, Do DD, Alerci M, Segatto JM, Tutta P, et al. Late acute thrombotic occlusion after endovascular brachytherapy and stenting of femoropopliteal arteries. *J Am Coll Cardiol* 2003;**41**:409–12.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9.
19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
20. Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
21. Wyttenbach R, Corti R, Alerci M, Cozzi L, DiValentino M, Segatto JM, et al. Effects of percutaneous transluminal angioplasty and endovascular brachytherapy on vascular remodeling of human femoropopilteal artery: 2 years follow-up by noninvasive magnetic resonance imaging. *Eur J Vasc Endovasc Surg* 2007;**34**:416–23.
22. Wyttenbach R, Gallino A, Alerci M, Mahler F, Cozzi L, DiValentino M, et al. Effects of percutaneous transluminal angioplasty and endovascular brachytherapy on vascular remodelling of human femoropopliteal artery by noninvasive magnetic resonance imaging. *Circulation* 2004;**110**:1156–61.
23. Waksman R. An update on peripheral brachytherapy. *Endovasc Today*:43–9. Available from: http://bmctoday.net/evtoday/pdfs/et1004_F2_Waksman.pdf; October 2004 [accessed July 5, 2011].
24. Serrano Jr CV, Ramires JA, Venturinelli M, Arie S, D'Amico E, Zweier JL, et al. Coronary angioplasty results in leukocyte and platelet activation with adhesion molecule expression. Evidence of inflammatory responses in coronary angioplasty. *J Am Coll Cardiol* 1997;**29**:1276–83.
25. Belch JJ, Shaw JW, Kirk G, McLaren M, Robb R, Maple C, et al. The white blood cell adhesion molecule E-selectin predicts restenosis in patients with intermittent claudication undergoing percutaneous transluminal angioplasty. *Circulation* 1997;**95**:2027–31.
26. Schillinger M, Mlekusch W, Wolfram RM, Budinsky AC, Exner M, Rumpold H, et al. Endovascular brachytherapy: effect on acute inflammatory response after percutaneous femoropopliteal arterial interventions. *Radiology* 2004;**230**:556–60.
27. Hopewell S, MacDonald S, Clarke M, Egger M. Grey literature in meta-analyses of randomized trials of healthcare interventions. *Cochrane Database Syst Rev* 2007;**2**:MR000010.